**ORIGINAL RESEARCH**

# To investigate and analyze the impact of calcium sulphate augmented with antibiotics in orthopaedic practice

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## ABSTRACT

**Aim:** The purpose of this research is to investigate and analyze the impact of calcium sulphate that has been supplemented with antibiotics in orthopaedic therapy. **Materials and Methods:** 50 Individuals who had been previously diagnosed with osteomyelitis, peri-prosthetic infection, or open fracture were invited to participate in the research. After obtaining the necessary permission, the participants in the research were recruited. The patients' clinical histories were recorded, and they were evaluated; preoperative laboratory values (TC, ESR, and CRP) were obtained; and radiographic examinations were carried out. Patients were evaluated using laboratory parameters (TC, ESR, and CRP), radiographs in anteroposterior and lateral views for resorption of calcium sulphate and bone healing, which comprised the basis line of the research. Patients were followed up-to 8 weeks, 4 months, and 8 months postoperatively. **Results:** 50 cases were included in our research, and each one was categorized into a specific type based on the ailment. There were 10 cases of osteomyelitis, 25 cases of periprosthetic fracture, 13 cases of open fracture, and 2 cases of de-gloving injury to the left leg. All of the cases were grouped together into our study. Each patient was given a preoperative evaluation before undergoing the surgical procedure, which consisted of the administration of one gram of vancomycin-impregnated calcium sulfate pellets. Eight months of follow-up were performed on each of the patients. In 45 of the instances, we had successful outcomes. 5 of the cases were deemed unsuccessful. In cases of osteomyelitis, peri-prosthetic infection, and open fracture, laboratory parameters with statistically significant P values were observed in TC, ESR, and CRP as follows: osteomyelitis (0.01, 0.01, 0.001) Peri-prosthetic infection (0.001, 0.001, 0.001) and in open fractures(0.001, 0,002,0.001) were noted. **Conclusion:** When applied topically at the site of an infection, antibiotic-impregnated calcium sulfate promotes bone healing and plays an important part in the fight against the infection, according to the findings of the research that we carried out.

**Keywords:** Calcium sulphate, Antibiotics, Rrthopaedic Practice,



## INTRODUCTION

Because of the extensive amount of time needed for therapy and the dismal outlook, chronic osteomyelitis has always been a challenging issue in the medical specialty of orthopedic surgery. The three main factors that contribute to the development of chronic osteomyelitis are acute hematogenous osteomyelitis, post-traumatic infection (particularly after internal fixation), and infection of the soft tissue [1,2]. During the surgical treatment procedure, thorough debridement serves as the most important step, and this approach always results in increased bone defects [3-5]. Staphylococcus aureus is one of the most often found bacteria that is associated with osteomyelitis. In order to treat osteomyelitis, not only must the damaged bone be reconstructed, but also the infection must be effectively controlled over an extended period of time.

It is vital to stabilize an open fracture or bony defect that has occurred and bone loss caused by infections such as osteomyelitis in order to lessen the discomfort, reduce the risk of neurovascular injuries and soft tissue damage, speed up the healing of wounds, and promote bone healing. It is difficult to remove or cure the osteomyelitis infection owing to the intricacy of the diagnostic process, the nature of the ailment, the amount to which it has spread, and the treatment strategy [6].

More recently, the treatment of open fractures primarily with internal fixation has shown

encouraging results [7], but there is still controversy regarding the possibility that internal fixation may increase the risk of infections due to bacterial adherence and biofilm formation on the surface of metallic implants [8]. In cases of peri-prosthetic infections, it might be challenging to eradicate the infective focus, which raises the question of whether or not the implant should be kept in place.

The current treatment for open fractures along with post-traumatic or post-operative osteomyelitis/infections, contaminated wounds requires thorough surgical debridement, elimination of dead space formed by bone loss & microbial infection, systemic antibiotics for longer duration in combination with local release of antibiotic obtained by implantation of the bio-absorbable materials such as Calcium sulphate, bone graft substitutes [9-20], and non-absorbable materials such as Polethylene glycol.

Despite the fact that systemic antibiotic therapy is the recommended course of treatment for open fractures and local infections, local antibiotic administration has been found to be effective in treating both conditions extremely well [21-27]. Calcium sulfate combined with antibiotic-impregnated polymethylmethacrylate (PMMA) is also utilized for initial stabilizations and to fill the defect in open fractures that have experienced bone loss [28- 30]. Calcium sulfate offers a number of benefits that set it apart from other local ways of antibiotic administration.

In addition to assisting in the process of osteoconduction, which is the production of new bone, it also helps to replace the void left behind when bone is lost as a result of disorders such as infection, trauma, or surgical procedures. Patients are need to undergo long term therapy since there has been a rise in the frequency of instances with complicated trauma and persistent orthopaedic infections (which may or may not benefit the patient). Patients who need long-term therapy must contend with additional co-morbidities, which not only hinders their morale but also their overall prognosis. In cases where an orthopaedic infection has already been established, osteomyelitis can be used to completely eradicate the infection, thereby avoiding the need for surgery. This can help reduce morbidity, as well as provide a treatment plan that is both cost-effective and does not place an additional burden on the patient.

## MATERIALS AND METHODS

50 Individuals who had been previously diagnosed with osteomyelitis, peri-prosthetic infection, or open fracture were invited to participate in the research. After obtaining the necessary permission, the participants in the research were recruited. The patients' clinical histories were recorded, and they were evaluated; preoperative laboratory values (TC, ESR, and CRP) were obtained; and radiographic examinations were carried out. Patients were evaluated using laboratory parameters (TC, ESR, and CRP), radiographs in anteroposterior and lateral views for resorption of calcium sulphate and bone healing, which comprised the basis line of the research. Patients were followed up-to 8 weeks, 4 months, and 8 months postoperatively.

## METHODOLOGY

Based on the medical professional's diagnosis of the ailments like as:

Open fractures that have resulted in bone loss, whether or not an infection has yet developed. Infections that were already present following the main fracture fixation, whether it was for an open or closed fracture (periprosthetic postoperative infections). Osteomyelitis, either acute or chronic.

Examinations of the patient's hematology, microbiology, and radiology were carried out as part of the preoperative assessment and investigation that was carried out. The purpose of the treatment protocol was to determine whether or not the local application of antibiotic-impregnated calcium sulfate beads containing vancomycin could be useful in the prevention and eradication of infection as well as the promotion of the healing process of wounds and [in the healing of bony defect and fracture union with the assistance of systemic or oral antibiotics in combination in the treatment of open contaminated fractures, established postoperative (periprosthetic) acute infections, and acute or chronic osteomyelitis].

## TREATMENT

We made use of the synthetic calcium sulfate that is currently on the market. We mixed 5 to 10 grams of calcium sulfate with 1 gram of vancomycin powder, then we molded the mixture into small pellets and placed them at the site of the infection, bone void formed at the fracture site, and in cases of osteomyelitis. Surgical debridement of the wound consists of resection of the soft tissues, thorough curettage, a full wash, prevention of vascularity in open fractures, filling the defect formed due to bone loss with calcium sulphate with or without PMMA antibiotic loaded cement, and internal fixation with plate and screws. In a small number of cases of open wound with severe bone loss, primary stabilization of the fracture with an external fixator and thorough surgical debridement, filling the defect formed with calcium sulphate augmented with 1 gm of vancomycin, and covering the soft tissue defect with vascularized muscular flaps or split skin graft are performed to assist in the healing process. When dealing with cases of acute periprosthetic infections that developed immediately after primary fixation, treatment options include debridement, retention or removal of the implant depending on the radiological signs, excision of the infection tract, and removal of potential causes for local infections in combination with systemic antibiotics for a longer duration. In situations of acute or chronic osteomyelitis, drainage of pus, debridement, and curettage of the diseased

bone or soft tissue, as well as filling the defect generated with antibiotic-loaded calcium sulphate beads and culture-sensitive systemic antibiotics for a longer time, are all treatment options.

**POST - OPERATIVE PROTOCOL**

Hematological investigations, such as a CBC, ESR, and CRP, should be performed postoperatively at 4 weeks, 8 weeks, 4 months, and 8 months. The patient had a second clinical examination in order to examine the surgical site and look for any symptoms of infection. An inspection of the area around the surgical incision to look for any discharge of pus or fluid. Following surgery, the wound was examined and dressed on a regular basis, parenteral antibiotics were administered at first, followed by oral antibiotics based on the results of a culture and sensitivity test performed on the particular organism, and anti-inflammatory analgesics were administered for additional symptomatic relief.

Postoperative radiographs were obtained to rule out the possibility of an infection, the resorption of calcium sulphate, and to look for radiographic evidence of bone healing, rebuilding, and stability at the operated site. After that, the process of mobilization began with the use of final fixation treatments for fractures and supportive measures for various illnesses.

**RESULTS**

50 cases were included in our research, and each one was categorized into a specific type based on the ailment. There were 10 cases of osteomyelitis, 25 cases of periprosthetic fracture, 13 cases of open fracture, and 2 cases of de-gloving injury to the left leg. All of the cases were grouped together into our study. Each patient was given a preoperative evaluation before undergoing the surgical procedure, which consisted of the administration of one gram of vancomycin-impregnated calcium sulfate pellets. Eight months of follow-up were performed on each of the patients. In 45 of the instances, we had successful outcomes. 5 of the cases were deemed unsuccessful.

**Table 1.Types of cases**

| | **Number** | **%** |
|---|---|---|
| Osteomyelitis | 10 | 20 |
| Periprosthetic fracture | 25 | 50 |
| Open fracture | 13 | 26 |
| De-gloving injury | 2 | 4 |

In 13 instances of open fractures, we were able to achieve a control rate of infection of one hundred percent; in ten instances, we were able to see satisfactory bone healing; and three instances required further reconstructive procedures. In one instance of an open fracture, we used an antibiotic-loaded PMMA cement spacer to fill the bony defect caused by bone loss at the time of the trauma. This was done in conjunction with calcium sulfate augmenting the internal fixation and primary closure at the primary stage. During the secondary stage, the cement spacer was removed. And another case of a compound fracture at the distal end of the femur and the proximal end of the tibia that had been treated with an external fixator, a muscle pedicle graft, and a skin graft was re-operated on after the infection was completely under control in order to realign the fracture fragment in the subsequent stage.

In addition to the antibiotics that were administered for a longer length of time, 21 out of 25 instances of peri-prosthetic infection were effectively treated and recovered within the allotted time period of 8 months. All of the wounds had totally healed, although there were still traces of irritation. Two cases of peri-prosthetic infection following postoperative total knee arthroplasty ended in failure due to the presence of antibiotic-resistant organisms. These cases required additional surgical procedures, including the removal of the implant, the application of antibiotic-loaded PMMA cement spacers, and the covering of the soft tissue defect formed over the knee with a rotational musculocutaneous flap. Two cases of periprosthetic infection were treated with cylinder casts for added stability because the implants had become loose as a result of unintentional weight bearing a few days after surgery. 2 of the cases failed to improve and the patients passed away during the course of treatment owing to medical complications and the development of septicemia in the patient. Following up on ten instances of osteomyelitis, researchers found that two patients with tuberculous osteomyelitis made a full recovery following eight months of treatment with AKT in conjunction with surgical debridement and the administration of vancomycin-impregnated calcium sulfate. Seven further instances of osteomyelitis that were followed up on showed signs of having made a full recovery. One patient's osteomyelitis of the calcaneum did not respond to treatment and ultimately necessitated an amputation as a result of uncontrolled diabetes and peripheral vascular disease.

In cases of osteomyelitis, peri-prosthetic infection, and open fracture, laboratory parameters with statistically significant P values were observed in TC, ESR, and CRP as follows: osteomyelitis (0.01, 0.01, 0.001) Peri-prosthetic infection (0.001, 0.001,0.001) and in open fractures(0.001, 0,002,0.001) were noted.

In general, the wounds healed well in the majority of the instances, and there were no evidence of infection or inflammation. The majority of patients who had open fractures or postoperative peri-prosthetic

infections exhibited signs of excellent bone healing in a period of time that averaged out to be eight months. In most cases, the pellets of calcium sulfate were reabsorbed into the body in eight weeks. After the implantation of the calcium sulfate pellets, there was serous discharge in 5 of the instances; nevertheless, wound healing was noted in those cases within 4 weeks.

**Table 2: Laboratory parameter**

| | ESR | Total count | CRP<6 | CaSo4 Resorption |
|---|---|---|---|---|
| Pre operative | 52.69 | 21047.36 | - | - |
| ommediate post Op | 47.75 | 16587.59 | 6% | - |
| 4th weeks | 26.58 | 9687.14 | 22% | 36% |
| 8th weeks | 17.25 | 8748.87 | 38% | 80% |
| 4 months | 11.91 | 7698.19 | 80% | 100% |
| 8 months | 12.47 | 7789.96 | 96% | 100% |

## DISCUSSION

The treatment of open fractures may be difficult, and there are certain instances in which it may even be difficult to save the limb. In recent years, it has become clear that internal fracture fixation, as opposed to external fracture fixation, is the preferred method of fracture treatment due to the excellent outcomes that it has produced. On the other hand, infection is the complication linked with open fractures that occurs the most often, followed by nonunion and malunion. These issues need to be resolved in a manner that will lessen the likelihood of complications during the major operation itself. In orthopaedic treatment, the significance of antibiotics is readily apparent. First doses of intravenous antibiotics serve a significant role in preventing infection and restoring normal function. Antibiotics have been connected with a decrease in infection incidence from 13.9 to 2.3%; nevertheless, large doses of systemic antibiotics and prolonged treatment duration are necessary to achieve adequate local antibiotic level at the site of infestation for the purpose of eradicating the infection. The use of calcium sulfate and other bone graft alternatives as a biodegradable and biocompatible material has shown promising results in a few of the studies that have been carried out in the past. This local delivery mechanism of antibiotics has also shown promising outcomes. Because to the osteoconductive qualities it has, calcium sulfate may assist in the production of new bone and can help prevent the development of a possible infection-related problem.

Cai X and his colleagues [23] conducted a study on 28 patients who had an open fracture of a long bone and were treated with internal fixation. They assessed the bone healing process and the absorption of calcium sulphate. 26 of the patients were able to effectively follow the instructions. In 26 of the instances, there was no indication of any occurrence. In two of the instances, there was shown to be exudation. The average amount of time needed for calcium sulfate to be reabsorbed was 1.4 months, whereas the average amount of time needed for bone to repair was 5.8 months (range 4-9 months). According to the findings of the research, lowering the patient's risk of developing a deep infection by using a combination of internal fixation and vancomycin-impregnated calcium sulfate is effective. Helgeson et al. [7] reported in their study that they treated 17 combat-related open fractures along with antibiotic impregnated calcium sulphate in different bones. In 12 fractures with an average of 8.5(1-19 months) months of follow up, they demonstrated clinical and radiological evidence of fracture healing and consolidation. Five of the patients required amputation; three of them had persistent infections, and two of them had severe neurogenic pain.

Zalvarus CG and colleagues [24] used local antibiotics in open fractures and osteomyelitis with bioabsorbable and non-absorbable material. They discovered that the use of local antibiotic therapy is a safe technique, has high local concentration with minimal systemic levels, and eliminates the need for reoperation and removal. In their investigation on 109 patients with bone abnormalities, Zhao Z et al. [36] looked at the effects of trauma, peri-prosthetic bone loss, tumors, and fusions on the patients' bones. Just calcium sulfate on its own was put to use. They observed that 99% of the calcium sulfate had been absorbed within 6 months, and that 88% of the defect had been filled with trabeculated bone by the time they did their follow-up after 12 months. There were four instances that showed complications.

In our study of open fractures, where 13 cases were studied, which were treated with internal fixation and antibiotic loaded calcium sulphate application, all cases had complete calcium resorption by 4 months with an average resorption time of 8 weeks. Ten of the cases of open fracture showed complete union by an average of 8 months, where 2 cases were re-operated for corrective surgeries, and 1 case with realignment of the fracture fragment. Another patient had surgery to repair a bone lesion in their femur using a vascularized fibular graft. Every single one of the treated instances of fracture showed signs of full wound healing. Because of this, our research replicated the findings of the aforementioned investigations, which found that antibiotic-loaded calcium sulphate assists in the management of infections and the regeneration of new bone in instances of open fractures that are properly treated.

Peri-prosthetic joint infections provide a challenge for orthopaedic practitioners since it is difficult to eradicate the infection completely and there is a need for ongoing follow-up care. It is possible that the patient might lose a limb or perhaps their life as a result of this. Edward J. McPherson and colleagues [35] used vancomycin and tobramycin in their research on the use of dissolvable antibiotic beads in the treatment of periprosthetic joint infections and revision arthroplasty. They found successful results in most of the cases, with a failure percentage of 3.2% in cases where drainage from the surgical wound was present. This was evident with the use of a higher volume of antibiotic beads. In 1.2% of instances, there was evidence of heterotopic bone development. There were only nine cases of infection-related failure out of a total of 250. In instances of revision joint situations, they discovered antibiotic-loaded synthetic calcium sulphate beads to be a suitable delivery method for local antibiotics.

In the study conducted by Fleiter N. et al. [33], the researchers examined 20 cases of posttraumatic or postoperative bone infection in which they used antibiotic-loaded calcium sulphate after radicle debridement. They looked at wound healing, infection parameters (lab parameters), resorption of calcium sulphate beads, and bone union. What they discovered was that the material used was safe and that there was no recurrence of infection.

Toms AD et al. [22], in their three-year study on 140 total hip arthroplasty patients, found infection rate in 7-16% of those who underwent revision. They also found that an increased level of ESR (erythrocyte sedimentation rate/hour)>30 and CRP (C reactive protein.)>10mg/l, have probability of infection rate in 83% of cases, and when both are negative, infection may be reliably excluded. This study was conducted in the United Kingdom.

In the research that we conducted, out of a total of 25 instances of peri-prosthetic infection, 21 patients were able to recover effectively within the allotted time period of 8 months, in addition to receiving antibiotics for a longer amount of time. All of the wounds had totally healed, although there were still traces of irritation. Two cases of peri-prosthetic infection following postoperative total knee arthroplasty ended in failure due to the presence of antibiotic-resistant organisms. These cases required additional surgical procedures, including the removal of the implant, the application of antibiotic-loaded PMMA cement spacers, and the covering of the soft tissue defect formed over the knee with a rotational musculocutaneous flap. Two cases of periprosthetic infection were treated with cylinder casts for added stability because the implants had become loose as a result of unintentional weight bearing a few days after surgery. In most cases of acute osteomyelitis, a good cure can be achieved with antibiotic therapy; however, the condition should be diagnosed early so that treatment can begin as soon as possible. This is despite the fact that antibiotics and surgical techniques have advanced significantly in recent years. Surgery and antibiotic treatment are both components of the treatment plan for patients with persistent osteomyelitis. Surgical debridement has the potential to produce favorable outcomes when combined with the administration of a local antibiotic and the application of bioabsorbable and nonabsorbable material that has been fortified with antibiotics. Bone graft substitutes are another tool that can be utilized to help achieve the desired outcomes.

Mc Nally et al. [34] conducted research on 100 instances of osteomyelitis, 81 of which occurred after an accident or surgical procedure. Patients were observed for an average of 19.5 months. It was concluded that a single stage surgical protocol along with absorbable local antibiotics is effective and offers patient friendly treatment. The infection was eradicated in 96 patients with single stage procedures, 4 cases had a recurrence which was successfully managed in a second surgery, adverse effects were noticed as fractures in 3 cases, 6 wound leaks, and 3 deaths unrelated to the infection, and it was concluded that the adverse effects were manageable.

Yan RJ et al. [28], in single stage compound grafting of antibiotic impregnated calcium sulphate and autologous cancellous bone for the treatment of chronic osteomyelitis in 52 cases in period of 2 years and followed them for average 2.8 years (2-3.8yrs), noticed primary healing was achieved in 52 cases, with only two cases experiencing a recurrence of the condition. Bone healing was acquired in 1.5-3.5 months (avg. 2.5 months), total radiographic absorption of calcium sulphate was achieved in 1.2- 3 months (avg. 2.2 months), and the persistence of the drain was seen in 10 instances for a period of between 2 and 3 months. The mean score for Maryland was 88.15 plus or minus 7.70 points. There were 32 instances with great outcomes, 14 cases with good results, and 6 cases with fair results.

In the population of 193 patients with osteomyelitis that Ferguson et al. [32] studied, all of whom had undergone surgical debridement and received an antibiotic carrier made of bio-absorbable calcium sulphate, the researchers analyzed the data to determine the rate of infection, the amount of bone that was filled in, and the rate at which wounds healed. There was no sign of recurrent infection in any of the study groups, and the researchers discovered that the infection had cleared up in virtually all of the patients. Nevertheless, thirty of the cases exhibited persistent bleeding. Defect formed after debridement, with complete healing occurring in 4.4% of cases, partial healing occurring in 59.1% of cases, and no healing occurring in 36.6% of cases, demonstrating that there is variability in bone defect filling.

## CONCLUSION

When applied topically at the site of an infection, antibiotic-impregnated calcium sulfate promotes bone healing and plays an important part in the fight against the infection, according to the findings of the research that we carried out. The findings over a shorter period of time are promising, but more investigation over a longer period of time is necessary in order to determine the efficacy of the locally applied calcium sulfate in the long-term elimination of the infection.

## REFERENCES


1. Beck-Broichsitter BE, Smeets R, Heiland M. Current concepts in pathogenesis of acute and chronic osteomyelitis. Curr Opin Infect Dis 2015;28:240-5.
2. Malkawi H, Shannak A, Sunna' P. Active treatment of segmental defects of long bones with established infection. A prospective study. Clin Orthop Relat Res 1984;184:241-8.
3. Haas DW, McAndrew MP. Bacterial osteomyelitis in adults: Evolving considerations in diagnosis and treatment. Am J Med 1996;101:550-61.
4. Kavanagh N, Ryan EJ, Widaa A, et al. Staphylococcal osteomyelitis: Disease progression, treatment challenges, and future directions. Clin Microbiol Rev 2018. doi: 10.1128/CMR.00084-17.
5. Kurien T, Pearson RG, Scammell BE. Bone graft substitutes currently available in orthopaedic practice. Bone Joint J 2013;95-B:583-97
6. Frosberg JA, Potter BK, Cierny G, Webb L. diagnosis and management of chronic infection. J AM Acad orthop surg 2011;19(1):S8-19.
7. Helgeson M, Potter B, Tucker C, Frisch HM. Antibiotic impregnated calcium sulphate use in combat related open fracture. Orthopedics 2009;32:323.
8. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilm: common cause of persistent infection. Science 1999;284:1318-22.
9. Malle GE. The use of antibiotic loaded synthesized calcium sulphate pellets in theone stage treatment of osteomyelitis, paper presented at:annual open scientific meeting of musculoskeletal infection society, proceeding of the 19th meeting of skeletal infection society august 7-8. San Diego California 2009
10. Mousset B, Benoit MA, Delloy C, Banillet R, Gillard J. Biodegradable implants for potential use in bone infection. An invitro study of antibiotic loaded calcium sulphate. International orthopaedic 1995;19:157-61.
11. Thomas MV, Puleo DA, Al- Sabbagh M. calcium sulphate:a review. J long termeffect med implants 2005;15(6):5999- 607.
12. Thomas DB, Brooks DE, Wenke JC, Bice TG, lonergan KT. Tobramycin impregnated calcium sulphate prevents infections in contaminated wounds. Clin orthop relat res 2005;441:366-71.
13. Sulo L, use f gentamicin impregnated plaster of paris beads in treatment of bone infection. Revue de cherugie orthopedique 1993,79,299-305.
14. Papagelopoulous PJ, Mavrogenis AF, Tsiodras *et al*. calcium sulphate delivery system with tobramycin for treatement of chronic psteomyelitis. The journal of international. Medical research 2006;34:704-712.
15. Pietrzak WS, Ronk R. Calcium sulphate bone void filler:a review and look ahead, journal of craniofacial surgery 2000;11(4):327-333.
16. Lalidau F. bone infection and bone graft substitutes for local antibiotic therapy.
17. Bowyer GM, Cumberland N. Antibiotic release from the impregnated pellets and beads. The journal of trauma 1994;36:3331-5.
18. Raushmann MA, Wichelhaus TA, Stirnal V, Dingeldein E, Zichner L, Schetner RA. Nanocrystalline hydroxyapatite and calcium silphate as biodegradable composite carrier material for local delivery of antibiotics in bone infections. Biomaterials 2005;26(15):2677-84.
19. Chang W, Colangeli M, Colangeli S, Dibella C, Gozzi. Donati D. Adult osteomyelitis; debridement vs debridement plusosteoset T pellets. Acta orthop Belg 2007;73:238-43.
20. Canavese F. Successful treatment of chronic osteomyelitis in children with debridement, antibiotic laden cement spacer and bone graft substitute. Eur. J Ortho. Surg. Traumatol 2017.
21. Dacquet V, Varlet A, Tandogan RN *et al*- antibiotic impregnated plaster of paris beads. Trails with Teicoplanin. Clinical orthop rel res 1992;282:241-9.
22. Toms AD, Davidson D, Masri MA, The management of periprosthetic infection in total joint arthroplasty. The journal of bone and joint surgery. British. 2006:88(2):149- 155.
23. Cai X, Han K, Cing K, Cai J, tong D, Han D *et al*. The use of calcium sulphate impregnated with vancomycin in the treatement of open fracture of long bone: a preliminary study. Orthopedics 2010;33(3). doi
24. Zalvarus CG, Patzakis MJ, Webb JJ, Holtom P. local antibiotic therapy in treatement of open fractures and osteomyelitis. Clin orthop relat res 2004;427:86-93.
25. Turner TM, Urban RM, Hall DJ, Chye PC, Segreti J, Gitelis S. local systemic levels of tobramycin delivery from calcium sulphate bone graft substitute pellets. Clin ortho relat res 2005;437:97-104.
26. Bibbo C. DV Patel- the effect of demineralized bone matrix calcium sulphate with vancomycin on calcaneal fracture healing and infection rates:prospective study.
27. Drosos GE, Baboura EC, Ververidid A, Kalkagia D, Veretas DA. Calcium sulphate cement in contained traumatic metaphyseal bone defects. Surg technol. Int. 2012;22:313-319.
28. Yan RJ. one stage compound grafting of antibiotics impregnated calcium sulphate and autologous cancellous bone for the treatement of chronic calcaneal osteomyelitis- Zhoungguo GU, Shang
29. Evans RP, Nelson CL. Gentamycin – impregnated PMMAbead compared with systemic therapy in the treatment of chronic osteomyelitis. Clinical orthopaedic related research 1993, 295.
30. Henry SI, Hood G, Seligson D. long term implantation of gentamicin PMMA beads- clinical orthopedics and rela res 1993;295:47-53.
31. McLaren AC, Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopedic infections. Clin orthop relat res 2004;427:101-106.
32. Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA. The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. Bone Jt J. 2014;96-B(6):829-36.
33. Fleiter N, Walter G, Bösebeck H, Vogt S, Büchner H, Hirschberger W, *et al*. Clinical use and safety of a

novel gentamicin-releasing resorbable bone graft substitute in the treatment of osteomyelitis/osteitis. Bone Jt Res 2014;3(7):223-9.
34. McNally M, Small J, Tofighi H, Mollan R. Two-stage management of chronic osteomyelitis of the long bones. The Belfast technique. J Bone Joint Surg Br. 1993;75- B(3):375-80.
35. Edward McPherson MF, Matthew Dipane BA, Sherif Sherif MD. Dissolvable Antibiotic Beads in Treatment of Periprosthetic Joint Infection and Revision Arthroplasty - The Use of Synthetic Pure Calcium Sulfate (Stimulan®) Impregnated with Vancomycin & Tobramycin. Reconstr Rev [Internet] 2013, 19. [cited 2019 Jul 21];3(1).
36. Zhao Z, Wang G, Zhang Y, Luo W, Liu S, Liu Y, Zhou Y, Zhang Y. The effect of calcium sulfate/ calcium phosphate composite for the treatment of chronic osteomyelitis compared with calcium sulfate. Ann Palliat Med 2020;9(4):1821-1833